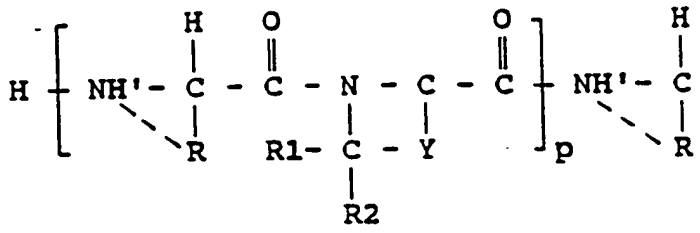
INHIBITORS OF DIPEPTIDYL-AMINOPEPTIDASE TYPE IV

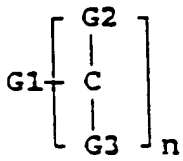
Abstract of the Disclosure

An inhibitory compound having the structure: Group I - Group II. Group I has the structure:

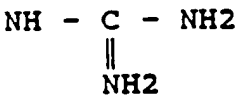


where H represents a hydrogen; C represents a carbon; O represents an oxygen; N represents a nitogen; each R, independently, is chosen from the group consisting of the R groups of an amino acid, including proline; each broken line, independently, represents a bond to an H or a bond to one R group, and each H' represents that bond or a hydrogen; and p is an integer between 0 and 4 inclusive.

Alternatively Group I has the structure:



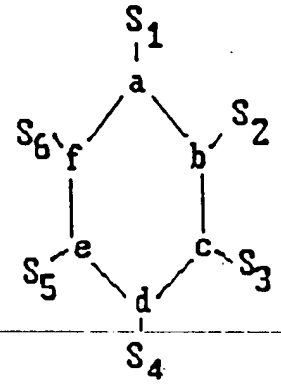
where n is between 0 and 3 inclusive, each G2 and G3 independently is H or C1 - 3 (one to three carbon atoms) alkyl, G1 is NH3 (H3 represents three hydrogens),



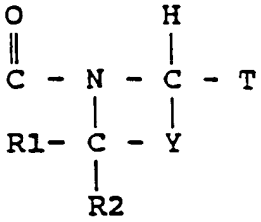
(H2 represents two hydrogens), or

NG4, where G4 is 

where G5 and G6 can be NH, H, or C1 - 3 alkyl or alkenyl with one or more carbons substituted with a nitrogen. G1 bears a charge, and G1 and Group II do not form a covalently bonded ring structure at pH 7.0. Group I may also have the structure:

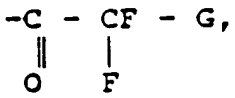


where one or two of the a, b, c, d, e, and f group is N, and the rest are C, and each S1 - S6 independently is H or C1 - C3 alkyl. Group I may also include a five membered unsaturated ring having two nitrogen atoms. Group II has the structure:

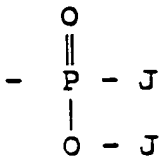


where T is a group of the formula:

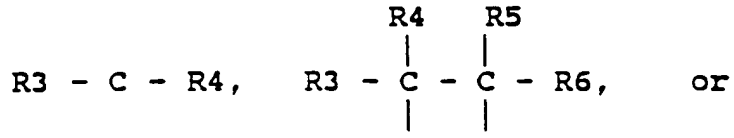
- B - D1, where each D1 and D2, independently, is a hydroxyl group or a group which is capable of being hydrolysed to a hydroxyl group in aqueous solution at physiological pH; a group of the formula:

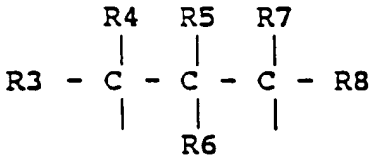


where G is either H, fluorine (F) or an alkyl group containing 1 to 20 carbon atoms and optional heteroatoms which can be N, S (sulfur), or O; or a phosphonate group of the formula:



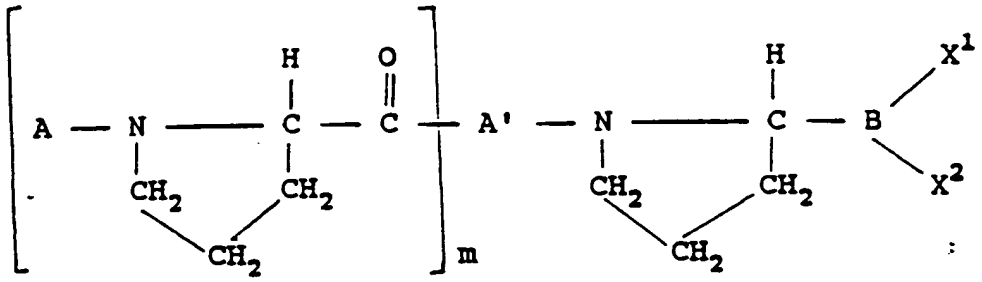
where each J, independently, is O-alkyl, N-alkyl, or alkyl. Each O-alkyl, N-alkyl or alkyl includes 1 - 20 carbon atoms and, optionally, heteroatoms which can be N, S, or O. T is generally able to form a complex with the catalytic site of a DP IV.

Y is 



and each R1, R2, R3, R4, R5, R6, R7, and R8, separately is a group which does not significantly interfere with site specific recognition of the inhibitory compound by DP IV, and allows a complex to be formed with DP IV.

In another aspect, the invention features an inhibitor of DP-IV, having the structure:



wherein m is an integer between 0 and 10, inclusive; A and A' are L-amino acid residues such that the A in each repeating bracketed unit can be a different amino acid residue; the C bonded to B is in the L-configuration; the bonds between A and N, A and C, and between A and N are peptide bonds; and each X^1 and X^2 is, independently, a hydroxyl group or a group capable of being hydrolysed to a hydroxyl group at physiological pH.